

***Remarks***

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 4, 6, 8, 9 and 11 are pending in the application, with claims 1 and 8 being the independent claims. Claims 3, 5, 7 and 9 have been delete without prejudice or disclaimer of the subject matter therein. Claims 1, 8 and 11 have been amended to further clarify the subject matter of the present invention. Support for these amendment can be found in the previously presented claims 1 and 3-7. Accordingly, this change does not add any new matter, and its entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Rejections under 35 U.S.C. § 103***

The Examiner has rejected claims 1 and 3-7 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chandran *et al.* (U.S. Pat. No. 6,890,957 B2, hereinafter "the '957 patent") in further view of Moeckel *et al.* (U.S. Pat. No. 5,955,106, hereinafter "the '106 patent") and Ghebre-Sellassie *et al.* (U.S. Pat. No. 6,499,984 B1), hereinafter "the 984 patent"). (Office Action, hereinafter "OA," at pages 5-7.) The Examiner asserts that "[t]he term synergistic combination of glimepiride and metformin or a pharmaceutically acceptable salt thereof is construed to be coextensive characteristic of the composition wherein the weight ratio of glimepiride and metformin or pharmaceutically acceptable salt thereof is about 1/500 to about 2/500." (OA at page 6.) The Examiner further cites

the '106 patent for teaching an "improved method of preparing metformin solid dosage." (OA at page 6.) The Examiner cites the '984 patent for teaching "methods of preparing tablet forms of an antidiabetic drug, including glimepiride and metformin." (OA at page 6.) The Applicant respectfully traverses this rejection as it may apply to the presently amended claims.

The references cited by the Examiner do not disclose all of the elements of the present claims, specifically, the references do not disclose the glimepiride/metformin hydrochloride ratio of about 1/500. Thus, the Examiner has not satisfied the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984).

The factors to be considered under 35 U.S.C. § 103(a) are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and MPEP §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The critical role of the Office personnel as fact finders when resolving *Graham* inquiries has recently been emphasized by the Office within its published Examination Guidelines. *See Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International v. Teleflex Inc. Fed. Reg. 72:57526- 57535* (October 10, 2007), hereinafter "Examination Guidelines." To establish a *prima facie* case of obviousness it is not sufficient to merely combine individual elements known in the prior art if the results would not have been predictable to one of ordinary skill in the art (*see* Examination Guidelines at page 57529). Establishment of a *prima facie* case of

obviousness requires that the Examiner factually show that the references in combination teach all of the elements of the claims, as well as provide a reasoned articulation that the combination of elements would have been known to produce a predictable result.

***1) The '957 patent***

The '957 patent is directed to a *liquid composition* comprising metformin, the purpose of formulating metformin as a liquid is to more easily adjust the treatment dosage of metformin. The present invention is directed to a solid dosage formulation comprising metformin hydrochloride and glimepiride in a synergistic amount. (*See* paragraphs [0014 and 0073].) The Examiner has not established why a person of ordinary skill in the art would abandon the dosage-adjustable liquid formulation described in the '957 patent for a solid formulation as recited in the rejected claims.

There is no disclosure in the '957 patent that a metformin hydrochloride/glimepiride formulation demonstrates a synergistic effect at any dose combination. The '957 patent discloses a generic range of sulfonylurea to metformin at a weight ratio of 1/50 to 1/300, with the preferred range of 1/75 to 1/250. The '957 patent is silent with respect to a sulfonylurea/metformin hydrochloride formulation producing a synergistic effect of lowering blood glucose levels in a patient.

The '957 patent does not exemplify any sulfonylurea/metformin hydrochloride formulation. The '957 patent broadly discloses that any known sulfonylurea, which includes glimepiride, or any antihyperglycemic agent may be used in combination with metformin. The '957 patent discloses that the preferred sulfonylureas are glyburide and glipizide. Thus, the disclosure of the '957 patent would not direct the ordinary artisan to using glimepiride (*see* the '957 patent, col. 8 lines 1-17), especially in light of the

observation that not all metformin/sulfonylurea combinations exhibit a synergistic effect.

For example, a combination of metformin with glyburide at a ratio of 75:1 does not result in a synergistic lowering of blood glucose levels in a diabetic patient. (See U.S. Pat. Appl. No. 6,011,049 B2, Form PTO-892 of December 5, 2006, col. 16, lines 21-35.)

Illustrated in the following table is a comparison of the results observed with a combination of metformin plus glyburide with the results of the combination of the present invention:

	<b>Metformin 500 mg</b> (present invention)	<b>Glimepiride 1 mg</b> (present invention)	<b>Metformin + Glimepiride 500 mg / 1mg</b> (present invention)	<b>Metformin + Glyburide<sup>1</sup></b> 1500 mg / 20 mg (U.S. Pat. No. 6,011,049)
Glycosylated Hemoglobin -HbA <sub>1c</sub>	+0.06	+0.25	<b>-0.70</b>	+0.10
Fasting Plasma Glucose Levels	+0.75	+0.68	<b>-1.77</b>	+6.0

The ordinary artisan would expect that combining two components where each component individually is known to reduce blood glucose levels would result in the additive effect of both components. The ordinary artisan would also expect that if you take more of each component the effect would increase proportionally with increasing amounts of the drug. However, this is not observed with the combination of metformin plus glyburide. Metformin plus glyburide at significantly increased doses, 3x more metformin and 20x more sulfonylurea, does not have the an additive effect in lowering the glycosylated hemoglobin levels or fasting blood glucose levels, and does not possess a synergistic effect. Thus, synergy with the claimed combination, at the claimed ratios, in the present application is not predictable.

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<sup>1</sup> Glyburide is a sulfonylurea and a preferred embodiment of the '957 patent.

Here, the Applicant has unexpectedly discovered that the claimed solid formulations of metformin hydrochloride plus glimepiride in a range of 500:1 has a synergistic effect on reducing blood glucose levels in a diabetic patient. (See specification paragraphs [0012 and 0014].) The efficacy of the combination is greater than the additive effect of each individual component, thus, the effect is synergistic. (See specification paragraph [0012].)

***In making this obviousness rejection the Examiner fails to consider the unexpected results of the present formulation***

The Examiner asserts that "[t]he weight ratio of metformin to glimepiride recited in the instant claims (ranging from 500/1 to 500/2) is found to overlap with the teaching of Chanran *et al.*" (OA at pages 5-6.) The Examiner further asserts that "[t]he term synergistic combination of glimepiride and metformin or a pharmaceutically acceptable salt thereof is construed to be coextensive characteristic of the composition. (OA at page 6.) The Applicant respectfully traverses this rejection as it may apply to the presently amended claims. Specifically, Applicants have amended the claims to recite a glimepiride/metformin hydrochloride ratio of 1/500.

The Examiner is improperly making an inherent anticipation argument in the context of a 35 U.S.C. § 103(a) rejection. Not all metformin/sulfonylurea combinations exhibit a synergistic effect. As discussed above, a combination of metformin with glyburide at a ratio of 75:1 does not result in a synergistic lowering of blood glucose level in a diabetic patient. (See U.S. Pat. Appl. No. 6,011,049 B2, Form PTO-892 of December 5, 2006, col. 16, lines 21-35.) Thus, the '957 patent does not provide any information that would indicate that the combination of metformin plus glimepiride in the claimed ratios would predictably produce a synergistic result. The Applicant asserts

that the Examiner has failed to establish a *prima facie* case of obviousness based on the reference because there is no showing in the reference that this combination of metformin plus glimepiride predictably lowers blood glucose levels in synergistic manner. Even if a *prima facie* case of obviousness has been established, which it has not, Applicant respectfully contends that the unexpected result of the synergistic lowering of blood glucose levels in a patient using the claimed composition is sufficient to overcome this rejection.

***2) The '106 patent***

The '106 patent does not rectify the shortcomings of the '957 patent. The '106 patent does not disclose a solid formulation comprising metformin and glimepiride. The '106 patent discloses a method of compacting metformin into a solid dosage form. The '106 patent does not describe administering a solid composition of metformin in combination with glimepiride. Furthermore, the '106 patent is silent with regard to a synergistic effect upon the administration of a solid dosage form comprising a combination of metformin and glimepiride at any ratio.

***3) The '984 patent***

The '984 patent does not rectify the shortcomings of the '957 patent. The '984 patent at most discloses the production of tablets that can include metformin or glimepiride. The '984 patent does not disclose a solid dosage form comprising both metformin and glimepiride in a single dosage form. The '984 patent is silent with regard to showing a synergistic effect upon the administration of a solid dosage form comprising a combination of metformin and glimepiride at any ratio.

In summary, the Examiner has not demonstrated that the combination of references would lead the ordinary artisan to predictably arrive at a synergistic composition comprising a solid dosage form of metformin and glimepiride at the claimed ratios. To sustain a rejection based on obviousness requires a showing that only knowledge which was within the level of ordinary skill at the time the claimed invention was made is used, and does not include knowledge gleaned only from the Applicant's disclosure. *See In re McLaughlin*, 443 F.2d 1392 (CCPA 1971), and MPEP §2142. Here, the Applicant has established that the claimed solid dosage form of metformin and glimepiride the ratio of 500:1 has a synergistic effect on reducing blood glucose levels in a diabetic patient. (*See* specification paragraphs [0012 and 0014].) It is unexpected that the efficacy of the combination of metformin plus glimepiride is greater than the additive effect of the individual components. (*See* specification paragraph [0012].)

The Examiner is reminded that in order to provide a proper basis for establishing a *prima facie* case of obviousness the results of the combination of references must be predictable. Because, not all formulations comprising metformin and a sulfonylurea produce a synergistic effect the combination of references cannot be extrapolated to arrive at the presently claimed invention without applying knowledge gleaned from Applicant's disclosure.

Applicant respectfully requests reconsideration and withdrawal of this rejection.

***Rejections under 35 U.S.C. § 102***

The Examiner has rejected claims 1, 3-9 and 11 under 35 U.S.C. §102(b) as allegedly being anticipated by Timmins *et al.* (U.S. Pat. No. 6,031,004, hereinafter "the

'004 patent"). (OA at pages 7-8.) The Examiner asserts that the '004 patent discloses combinations of metformin and a sulfonylurea for treating patients with hyperglycemia. "[G]limpiride is disclosed as a preferred sulfonylurea antihyperglycemic agent for use in combination with the metformin, and wherein metformin/sulfonylurea are used in a ratio of 300/1 to about 50:1, preferably from about 250/1 to about 75:1." (OA at page 7.) Applicants respectfully traverse this rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants assert that the Examiner has not met their burden of establishing that all the elements are present in the '004 patent.

The metformin salts of the '004 patent are directed to metformin salts of dibasic acids, preferably dibasic organic carboxylic acids. (See the '004 patent, col. 1, ll. 8-10, Examples 1-10, and the claims.) While the present claims are directed to metformin hydrochloride. Thus, the '004 patent is missing the element of metformin hydrochloride. Additionally, the '040 patent discloses a metformin sulfonylurea urea ratio of about 300:1 to about 50:1. The present claims are directed to a metformin hydrochloride:glimepiride ratio of 500:1. Thus, the '004 patent is missing this additional element of a metformin hydrochloride:glimepiride ratio of 500:1. Applicants respectfully request reconsideration and withdrawal of this rejection.

### ***Conclusion***

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the

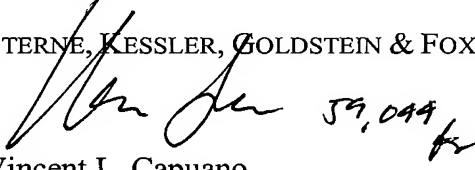


Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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